Emergency diagnosis and treatment of adult meningitis

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Despite the existence of antibiotic therapies against acute bacterial meningitis, patients with the disease continue to suffer significant morbidity and mortality in both high and low-income countries. Dilemmas exist for emergency medicine and primary-care providers who need to accurately diagnose patients with bacterial meningitis and then rapidly administer antibiotics and adjunctive therapies for this life-threatening disease. Physical examination may not perform well enough to accurately identify patients with meningitis, and traditionally described lumbar puncture results for viral and bacterial disease cannot always predict bacterial meningitis. Results from recent studies have implications for current treatment guidelines for adults with suspected bacterial meningitis, and it is important that physicians who prescribe the initial doses of antibiotics in an emergency setting are aware of guidelines for antibiotics and adjunctive steroids. We present an overview and discussion of key diagnostic and therapeutic decisions in the emergency evaluation and treatment of adults with suspected bacterial meningitis.

Introduction

A 25-year-old man presents to the emergency department with a chief complaint of fever, headache, and neck pain. It is a busy Saturday night in your emergency department and you are not made aware of the patient’s arrival for 20 min. An experienced member of your nursing staff approaches in the middle of your evaluation of a different patient with potential acute coronary syndrome to ask for an order for an antipyretic agent. When you learn that the patient’s temperature is 39·7ºC (103·5ºF), you immediately go to evaluate him. You become concerned about a life-threatening infection of the central nervous system when you find his examination notable for fever, somnolence, photophobia, and neck stiffness.

Many clinicians might feel that the initial medical treatment for a patient like this who presents with classic signs and symptoms of bacterial meningitis may be straightforward. The possibility of bacterial meningitis mandates rapid initiation of stabilising medical treatment and antibiotic administration. However, for the majority of patients who present for emergency evaluation with symptoms that could be caused by meningitis, the most appropriate steps for diagnosis and treatment will not be as immediately apparent.

The topics discussed in this review will focus on decisions that emergency medicine and primary-care physicians have to make when diagnosing and treating adult patients with suspected meningitis. The initial steps in evaluation typically focus on history and physical examination, and we will discuss the literature suggesting that much of this evaluation may not accurately identify meningitis. Decisions regarding neuroimaging before lumbar puncture and the interpretation of lumbar puncture results will be reviewed. Finally, we will examine the empiric treatment of presumptive bacterial meningitis with antibiotics together with adjunctive systemic steroids.

Epidemiology

The estimated incidence of bacterial meningitis per year is 0·6–4 per 100 000 adults in developed countries, and might be up to ten times higher in other parts of the world.1,4 Meningitis caused by Haemophilus influenzae type b has nearly been eliminated in many developed countries since routine childhood vaccination was initiated,7 and the introduction of conjugate vaccines against seven serotypes of Streptococcus pneumoniae has reduced the burden of childhood pneumococcal meningitis substantially.6,9 In some regions of the world, invasive infections caused by Neisseria meningitidis serogroup C have increased over the past 10 years, prompting the introduction of routine immunisation with serogroup C meningococcal polysaccharide–protein conjugate vaccines.8 The recent approval of a conjugate meningococcal vaccine against serogroups A, C, Y, and W135 might lead to a further decrease in the incidence of this devastating infection.10 As a consequence of these kinds of routine vaccination programmes in developed countries, the age-specific incidence of bacterial meningitis has decreased in children, thus increasing the fraction of patients that are adults.11 In 2005, the Netherlands Reference Laboratory for Bacterial Meningitis received 484 bacterial cerebrospinal fluid isolates from patients with meningitis and 56% were from patients older than 16 years of age.1 In these adults with community-acquired bacterial meningitis, the most common aetiologic agents now are S pneumoniae and N meningitidis, which cause 80–85% of all cases.1 This manuscript will focus on the diagnosis and treatment of meningitis, and readers are referred to other resources for details about systemic infections such as meningococcal sepsis.11,12

Initial evaluation of meningitis

Patient history, signs, and symptoms

In adult patients diagnosed with meningitis, little is known about the timeframe between the initial onset of symptoms and first consultation with a physician. A recent study provided a systematic assessment of the sequence and development of early symptoms in children and adolescents with meningococcal disease (encompassing the spectrum of disease from sepsis to meningitis) before admission to the hospital.9 Although limited by the retrospective design, this study showed that classic symptoms of rash, meningismus, and
impaired consciousness develop late in the pre-hospital illness, if at all. Early signs before admission in adolescents (ages 15–16 years) with meningococcal disease were leg pain (53%) and cold hands and feet (44%). Studies have not yet been published with similar data for adult patients.

When a patient presents to an emergency department physician, primary-care doctor, neurologist, or infectious disease specialist for an emergent evaluation, the patient history can help to estimate the probability of meningitis. A wide variety of patient complaints may be elicited from patients with meningitis, and a meta-analysis that included 845 patients over a 30-year period showed poor sensitivity and specificity for symptoms such as headache, nausea, and vomiting for the diagnosis of meningitis. This is not surprising since such non-specific symptoms are found in many patients suffering from a wide variety of clinical conditions.

To identify common features that might help to screen for meningitis in an emergency setting, a clinician may look to examine large retrospective studies of patients who were diagnosed with bacterial meningitis. A study from a tertiary hospital with 493 episodes of bacterial meningitis in adults showed that the historical “classic triad” of fever, stiff neck, and alterations in mental status was present in only two-thirds of adults. Fever was the most common finding (present in 95% of patients) and at least one element of the so-called classic triad was found in every single patient with meningitis. Other retrospective analyses of bacterial meningitis found a high incidence of fever (84–97%) associated with lower numbers of patients having the classic triad of symptoms (21–51%), or symptoms of fever, stiff neck, and headache (66%). Although a caveat for retrospective studies is that the absence of recorded symptoms does not necessarily mean these were not present, the findings from these large cohorts of patients demonstrate that there are certainly aspects of an initial patient presentation that should make clinicians suspect meningitis. The findings support an intuitive approach to differential diagnosis, but clinicians should be careful to note that signs and symptoms alone do not provide sufficient information to diagnose meningitis. However, one meta-analysis suggests that the absence of fever, neck stiffness, and altered mental status effectively eliminates meningitis as a likely diagnosis with a sensitivity of 99–100%.

A Dutch nationwide prospective study of 696 adults with community-acquired bacterial meningitis found an even lower incidence of 44% for the classic triad of fever, neck stiffness, and change in mental status (defined as a score on the Glasgow Coma Scale of 14 or less). This prospective cohort had a somewhat lower prevalence of fever (77%) in patients diagnosed with bacterial meningitis. However, the researchers did find that 95% of patients with culture-proven bacterial meningitis presented with at least two signs or symptoms of headache, fever, neck stiffness, and alterations in mental status. At least one of these four elements was present in 99% of patients, further supporting the idea that aspects of history and physical examination can be used to heighten suspicion of meningitis even if they cannot alone rule out the diagnosis.

Specific physical examination findings

How good are specific physical examination findings in helping to diagnose patients with suspected meningitis that was based on initial presentation? Although the traditionally described purpuric rash of meningococcaldisease would influence a clinician’s suspicion for meningitis caused by this pathogen, most adults with bacterial meningitis do not present with prominent skin findings—only 11% of cases (30 of 279) had a rash in a large retrospective series and only 26% of cases (176 of 683) had a rash in a prospective study. There are a number of other clinical findings that clinicians are taught in medical school to look for and evaluate in patients with signs and symptoms indicating meningitis, such as Kernig’s sign, Brudzinski’s sign, and meningismus. Many physicians who use these physical findings in their clinical decision-making might not be aware of the studies suggesting that these findings lack adequate sensitivity to be used in isolation to diagnose or exclude a potentially life-threatening disease.

The presence or absence of meningeal signs such as Kernig’s sign, Brudzinski’s sign, and nuchal rigidity are physical examination findings often documented when evaluating a patient for possible meningitis. Kernig’s sign was first described in the 1880s and was originally done with the patient in the sitting position, but today is frequently done in the supine position. This test involves flexing the hip and extending the knee and a positive result is recorded when pain is elicited in the back and legs. Brudzinski’s neck sign is typically done in the supine position where the head is passively flexed and is interpreted as positive when flexion at the hips to lift the legs is elicited in response. Nuchal rigidity is a clinical determination of severe neck stiffness and inability to passively flex and extend the head in a normal fashion.

So is the absence of these meningeal signs sufficient to rule out meningitis? A prospective study with 297 adults evaluated Kernig’s sign, Brudzinski’s sign, and nuchal rigidity and their relation to meningitis diagnosed by lumbar puncture. This study found that none of these signs accurately identified patients with meningitis. There was no correlation with moderate meningeal inflammation or with microbial evidence of infection (such as positive Gram stain or positive cultures), and Kernig’s sign and Brudzinski’s sign were found to have poor sensitivity (5%) with high specificity (95%). In this study population, 80 of 297 patients had meningitis, but only 24 had nuchal rigidity (sensitivity 30%). Nuchal rigidity was absent in 148 of the 217 patients without meningitis (specificity 68%). Notably, only three of the
297 patients (1%) had bacterial meningitis by cerebrospinal fluid culture, and nuchal rigidity failed to identify two of these three patients with bacterial meningitis.21

The jolt accentuation test is another clinical test for meningeal irritation that was evaluated in a prospective study of 54 patients with headache and fever in an effort to identify those with meningitis.22 This test is done by having the patient rotate his head in a horizontal fashion at a rate of two to three times per second, and a positive test is the exacerbation of an existing headache. The sensitivity of neck stiffness and Kernig’s sign were very poor (15% and 9%, respectively), whereas that of the jolt accentuation was 97% in their small patient cohort with specificity of 60%.22 Use of the jolt accentuation test has not been evaluated in any larger subsequent studies, but the overall results support that the absence of the traditionally described “meningeal signs” may not be sufficient to rule out meningitis.

Naturally, physicians do not rely on a single test for diagnosis and combine a number of historical and physical examination findings together to form a clinical impression. This approach is supported by the retrospective and prospective studies identifying patient characteristics concerning for meningitis and reveals the limitations of physical examination.2,3,16–20,21,22 When sufficient suspicion remains after a thorough history and physical examination, clinicians must consider further diagnostic testing.

Diagnostic lumbar puncture
Indications for computed tomography scan before lumbar puncture
Once an initial patient evaluation has been completed with history and physical findings, lumbar puncture is the diagnostic procedure of choice if the diagnosis of bacterial meningitis cannot be ruled out. Characteristic findings in the cerebrospinal fluid are typically used to make the diagnosis of meningitis. In view of the urgent nature of this testing to make the diagnosis of meningitis, one of the issues physicians are faced with in an emergency department setting is whether neuro-imaging—either computed tomography (CT) or magnetic resonance imaging (MRI)—is required before lumbar puncture. The possible role of MRI in the acute evaluation of patients with bacterial meningitis is unknown, and the time required to obtain MRI or other high-resolution methods of brain imaging at many centres make this an impractical technique for emergency use. CT scan is, therefore, used for this purpose in most institutions.

One fear that has been discussed in the literature since the first lumbar punctures were done in the late 1800s and early 1900s is the risk of herniation and possible death precipitated by lumbar puncture.23 Of primary concern is the occult presence of an intracranial mass lesion (such as a tumour or toxoplasmosis lesion) that could possibly lead to brain shift, which may end in herniation and death. Cranial imaging can be considered as a way to evaluate for signs of brain shift as a precaution in selected patients before lumbar puncture. Numerous papers over the past 125 years have tried to establish whether cerebral herniation is caused by lumbar puncture. There are several paediatric studies that show a possible temporal relationship between children with meningitis who had lumbar puncture and subsequently herniated,24–26 but also reports of patients with meningitis who had brain herniation even in the absence of a lumbar puncture procedure.24,27 Some reports have noted that a cranial CT may even be normal in some patients when completed just before impending herniation,25,27 but such cases are difficult to interpret in light of the limitations of CT scan for diagnosing brain herniation, imaging the posterior fossa, and predicting risk of complications after lumbar puncture.

There are several interesting case series that were published before CT scan was available to evaluate for mass lesions or possible signs of increased intracranial pressure. One review of 200 cases of lumbar puncture in patients with known increased intracranial pressure (144 had papilloedema) showed no adverse effect of diagnostic lumbar puncture in 200 patients with verified or suspected brain tumours.28 Another series of 103 patients with increased intracranial pressure who all had lumbar puncture found only four deaths within 6–40 h after lumbar puncture, but there was no herniation found at autopsy on three and an unclear causal relationship for any of them.29

Lumbar puncture completed on 56 patients with papilloedema reported no clinical changes in patient condition in one series,30 and another series of 70 patients with papilloedema reported one possible complication in a comatose patient with a skull fracture and seizures before lumbar puncture who died 15 h after the procedure was completed.31 In this same series, 59 patients with increased intracranial pressure but no papilloedema had an 11% incidence of complications within 48 h of lumbar puncture, but all were felt to have not been caused by the lumbar puncture itself.31 Papilloedema was rare in a large retrospective study including adults with bacterial meningitis (2–4% of patients)32 in the Dutch Meningitis Cohort,1 papilloedema was an uncommon finding present in only 13 patients of 386 examined by funduscopy (3%). In this study, unfavourable outcome was defined by a Glasgow Outcome Scale score of 1–4 points at discharge and favourable outcome was defined by a score of 5. Although papilloedema was related to unfavourable outcome (eight of 13 [62%] versus 103 of 373 [35%]; p=0.01), four patients who had papilloedema without any other contraindication to lumbar puncture were reported to have normal CT scans before lumbar puncture was performed (van de Beek D, unpublished data). This might suggest that the risk of acute herniation in the setting of papilloedema or increased intracranial pressure, or both, is perhaps not as high as feared in patients with bacterial meningitis, which might make the use of CT scan before lumbar puncture unnecessary in selected patients.
meningitis. Nevertheless, with the low incidence of papilloedema in meningitis, and considering that the funduscopic examination may be challenging to complete in some patients, routine ophthalmological examination might not be required in all patients that are considered for lumbar puncture. However, when papilloedema or other signs concerning for potential brain shift are identified, clinicians should recognize that lumbar puncture could potentially cause or hasten herniation, whether or not there is increased intracranial pressure or papilloedema. Therefore, in patients with suspected bacterial meningitis the interpretation of cranial imaging should be focused on brain shift, which may result from a focal space-occupying lesion or severe diffuse brain swelling as illustrated in figure 1.

Recommendations for cranial CT and fears of herniation are based on the observed clinical deterioration of a few patients in the several to many hours after lumbar puncture and the perceived temporal relationship of lumbar puncture and herniation, but as previously mentioned proving a cause and effect association is very difficult based on the available data. Many of these studies based their diagnosis of herniation on clinical signs alone without a radiographic or pathological confirmation of the diagnosis and clinicians are left with the realization that “herniation after lumbar puncture does not necessarily mean herniation caused by lumbar puncture.”

With these observations in mind, some authors have attempted to solve this problem in the setting of suspected meningitis. There are no unequivocal examples in the literature of patients who were neurologically normal before lumbar puncture who then suffered a devastating insult caused by this diagnostic test. Clinicians should use CT scan to detect evidence of brain shift, since almost all cases of bacterial meningitis have associated increases in cerebrospinal fluid opening pressures and yet herniation remains a rare complication overall.

Within all of this uncertainty, there remains the issue that there is possibly a small subset of patients whose clinical condition could acutely worsen if lumbar puncture were completed in the emergency department. One set of recommendations for emergency department brain CT scanning before lumbar puncture are based on a prospective study in 2001, which included 301 adult patients with suspected meningitis. Items associated with abnormal CT scan included: age more than 60 years, altered mental status, gaze or facial palsy, abnormal language or inability to answer two questions or follow two commands, immunocompromise, history of central nervous system disease, seizure in past week, visual field abnormalities, and arm or leg drift. In this cohort of patients, if none of these features were present there was a negative predictive value of 97% for an intracranial abnormality, confirming that clinical features can be used to identify patients who are unlikely to have abnormal findings on brain CT. Interestingly, there were a few patients in this study with abnormalities that were missed by these clinical criteria who ultimately underwent lumbar puncture without any apparent complications. It is also important to recognize that this study used CT scan abnormalities as a surrogate marker for increased risk of herniation.

We feel it is reasonable to proceed with lumbar puncture without a CT scan if the patient does not meet any of the following: patients who have new-onset seizures, an immunocompromised state, signs that are suspicious for space-occupying lesions (papilloedema or focal neurological signs [not including cranial nerve palsy]), or moderate-to-severe impairment of consciousness. The classification of patients as low risk for complications after lumbar puncture when they lack...
clinical features related to intracranial brain shift appears to be a reasonable approach to this difficult decision.

**Interpretation of lumbar puncture results**

When lumbar puncture is completed and findings show increased white blood cell counts in the cerebrospinal fluid, confirming a diagnosis of meningitis, many clinicians would like to determine which patients are at risk for the truly life-threatening bacterial meningitis versus those with a typically less concerning viral meningitis. The next topic that physicians evaluating patients in an emergency setting have to consider is whether or not cerebrospinal fluid findings can accurately predict the risk for bacterial disease.

It is important for providers to recognise that there have been several documented cases of bacterial meningitis in the absence of pronounced pleocytosis in the cerebrospinal fluid (ie, less than 100 white blood cells per µL found at the time of lumbar puncture). Keeping this in mind, lumbar puncture results might help to risk-stratify patients we are evaluating for potential meningitis. Table 1 reflects a common representation of typical findings in bacterial and viral meningitis that can be found in many textbooks and reference sources. Classically described, the white blood cell count in bacterial meningitis is typically greater than 1000 cells per µL, while in viral meningitis it is less than 300 cells per µL—although considerable overlap exists in these categories. The neutrophil count is typically elevated in bacterial meningitis compared with viral meningitis. The measurement of protein and glucose is an important aspect of cerebrospinal fluid analysis to complement the cell counts because abnormal protein and glucose levels are typically found in bacterial disease but are relatively normal in many cases of viral meningitis. Gram stain of cerebrospinal fluid samples, although having reported normal in many cases of viral meningitis, Gram stain of the cerebrospinal fluid (ie, less than 100 white blood cells per µL) at the time of lumbar puncture). Classically described, the white blood cell count in bacterial meningitis is typically greater than 1000 cells per µL, while in viral meningitis it is less than 300 cells per µL—although considerable overlap exists in these categories. The neutrophil count is typically elevated in bacterial meningitis compared with viral meningitis. The measurement of protein and glucose is an important aspect of cerebrospinal fluid analysis to complement the cell counts because abnormal protein and glucose levels are typically found in bacterial disease but are relatively normal in many cases of viral meningitis. Gram stain of cerebrospinal fluid samples, although having reported normal in many cases of viral meningitis, has been found to have positive Gram stains in 81–93% of cases. The diagnostic yields from Gram stain and subsequent culture may be decreased when previous antibiotic therapy has been given, although it is unlikely that the other biochemical and cellular abnormalities of cerebrospinal fluid would be affected by previous therapy.

There are several problems with using a chart such as Table 1 for clinical decisions on individual patients, particularly when determining whether patients require admission or can be discharged home. Much of the data in the literature concerning guidelines for predicting bacterial disease are derived from paediatric patients, and the data available for adult patients suggests that using such a strategy would miss a number of patients with bacterial disease. One retrospective study found that 5% of cases (27 of 493) with documented bacterial meningitis had a cerebrospinal fluid white blood cell count of less than 100 cells per µL, whereas three other retrospective analyses of bacterial disease found 10–19% of patients with a white blood cell count less than 100 cells per µL—a level many would consider predictive for viral disease. A prospective study of 696 patients with bacterial meningitis found that 12% of patients did not have any individual cerebrospinal fluid findings predictive for bacterial meningitis. Many studies in adults and paediatric patients have come to the conclusion that in the setting of an elevated white blood cell count in the cerebrospinal fluid, there is no single variable that can reliably rule out bacterial meningitis.

Perhaps clinicians can rely on combinations of cerebrospinal fluid findings to accurately predict bacterial disease? Despite multiple retrospective models using logistic equations and other mathematical modeling, none have yet proved robust enough for widespread clinical practice. The practice guidelines from the Infectious Diseases Society of America suggests that these prediction rules should not be used for clinical decisions in individual patients. One additional aspect of particular importance to physicians working in emergency medicine and other urgent outpatient settings is that all of the studies in adult patients were done on hospitalised populations. Therefore, in all of the studies evaluating the potential to differentiate bacterial and viral meningitis every patient was admitted to the hospital for observation regardless of whether they received antibiotics or not. One should use appropriate caution when attempting to apply these kinds of decision rules to patients that might be considered candidates for outpatient treatment with suspected viral meningitis. There are no well-designed studies available to assist clinicians with this particular disposition decision, and individual clinicians will have to decide what level of risk is tolerable when diagnosing someone with viral meningitis and considering them as possible candidates for discharge home with outpatient follow-up.

### Treatment for suspected bacterial meningitis

**Rapid administration of broad-spectrum antibiotics**

Bacterial meningitis is a neurological emergency and can lead to substantial morbidity and mortality. Recent prospective and retrospective studies document a mortality

**Table 1:** Classically described cerebrospinal fluid findings in bacterial and viral meningitis

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<th>Bacterial meningitis</th>
<th>Viral meningitis</th>
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<tr>
<td>White blood cell</td>
<td>1000–10 000</td>
<td>&lt;300</td>
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<tr>
<td>count (cells per µL)</td>
<td>Range &lt;1000–&gt;10 000</td>
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<tr>
<td>Neutrophils</td>
<td>&gt;80%</td>
<td>&lt;20%</td>
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<tr>
<td>Protein levels</td>
<td>Elevated</td>
<td>Normal</td>
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<td>Glucose levels</td>
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<td>Normal</td>
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See text for discussion of the reasons why these findings may not be adequate to predict the risk of bacterial disease in individual patients.
rate of 13–27% despite appropriate antibiotic therapy.3,17,19,37,59–61 Although there has not yet been a definitive study showing a clear beneficial timeframe for antibiotics,59,60,62 early antibiotic treatment in the emergency department may contribute to increased survival when compared with patients who do not receive antibiotics until after admission to the hospital.61 Although some guidelines attempt to propose an arbitrary time-based goal for antibiotic administration,4 others feel that a specific time point has not yet been identified as essential, but instead focus on level of disease severity and antibiotic administration as soon as possible once the diagnosis is considered.38,60,61

A prospective study involving 156 patients with pneumococcal meningitis who were admitted to the intensive care unit found that a delay of more than 3 h after presentation to the hospital for receiving antibiotics was independently associated with 3-month mortality.64 Future prospective studies will be needed to confirm whether this or another timeframe is found to be important for patients in all clinical settings. Whereas some publications advise community physicians to give parental antibiotics before transferring patients with suspected meningococcal meningitis to the hospital,63,65 conflicting studies make this recommendation difficult to endorse with available retrospective data.66–69 Until prospective data are available to support this practice,70 we suggest rapid administration of antibiotic therapy in the emergency department (figure 2 and table 2).

Several studies have identified sources of delay in antibiotic administration, the most important of which include waiting for CT scan, laboratory studies, or admission to the hospital.36,59,73 It is important to remember that the recommendations for CT scan include the caveat that patients who undergo CT first should have blood cultures and antibiotics started before ordering the CT scan.4

When initial choice of antibiotics is considered, practice guidelines and expert opinions recommend broad-spectrum coverage until bacterial identification can be obtained.3,4,38,63,65 The choice of initial antimicrobial therapy must be based on the most common bacteria causing the disease according to the patient’s age and the clinical setting, and local patterns of antimicrobial susceptibility.72 Empirical coverage with a third-generation cephalosporin (cefotaxime or ceftriaxone) at appropriate doses for meningitis is recommended, based on a broad spectrum of activity and excellent penetration into the cerebrospinal fluid during inflammatory conditions.74 The increasing prevalence of multidrug-resistant S pneumoniae in many parts of the world (as high as 35% in parts of the USA)75,76 has led most experts to recommend the addition of vancomycin to initial empirical therapy in adult patients.4,38,63 Additionally, patients over the age of 50 years should have ampicillin added to the above antibiotics for additional coverage of Listeria monocytogenes, which has a higher incidence in this age group.3,4,38,63 Table 2 summarises these recommendations.

Figure 2: Algorithm for the management of patients with suspected community-acquired bacterial meningitis

This material was previously published as part of an online supplementary appendix to reference 4. Copyright 2006 Massachusetts Medical Society. All rights reserved. CSF=cerebrospinal fluid.
Systemic steroid therapy to treat inflammation in suspected bacterial meningitis

Inflammation from any source in the central nervous system is poorly tolerated, and such inflammatory responses within the enclosed spaces of the brain and spinal cord have been shown to lead to destructive secondary effects in basic science models.77 In the case of bacterial meningitis, the cerebrospinal fluid is effectively sterilised a few hours after beginning appropriate antimicrobial therapy, and Gram stain and culture are often negative within hours of antibiotic administration.84 The intense inflammatory response to bacterial infection within the enclosed spaces of the brain and spinal cord is thought to lead to significant morbidity and mortality despite effective antibiotic therapy.77 Therefore, pharmacological attempts to modulate this inflammatory response may be an essential component of a successful strategy to treat this life-threatening disease, and dexamethasone is the only currently accepted adjunctive therapy for the treatment of patients with bacterial meningitis that has proven clinical efficacy. Several other adjunctive therapies have been described, which have been reviewed elsewhere.81

An important aspect of treatment for patients with suspected bacterial meningitis that emergency physicians must be familiar with is the use of intravenous dexamethasone to be given at the time of the first dose of antibiotics. For adult patients, there are several published studies in the literature that support the use of dexamethasone for bacterial meningitis,82–83 including a prospective, randomised, double-blind multicentre, placebo-controlled trial of 301 adults with bacterial meningitis.83 Dexamethasone (10 mg) or placebo was administered 15–20 min before or with the first dose of antibiotic and was given every 6 h for 4 days. The primary outcome measure was the score on the Glasgow Outcome Scale at 8 weeks after admission (a score of 5, indicating favourable outcome, versus a score of 1–4, indicating an unfavourable outcome). In this study, treatment with dexamethasone was associated with a reduction in the risk of an unfavourable outcome (relative risk [RR] 0.59; 95% CI 0.37–0.94) and with a reduction in mortality (RR 0.48; 0.24–0.96). In patients with pneumococcal meningitis, mortality was reduced from 34% to 14%, a result of reduced mortality from systemic causes.85 The benefits of adjunctive dexamethasone therapy were not undermined by increased neurological disability in patients who survived or by any steroid-induced complications.

A meta-analysis of 623 adult patients with bacterial meningitis showed an overall decrease in mortality and neurological sequelae by the use of adjunctive dexamethasone.86 A larger systematic review in the Cochrane Database including 1800 adults and children also demonstrates a substantial reduction in fatality, hearing loss, and neurological sequelae with steroid use in bacterial meningitis.87 Current practice guidelines and expert opinions recommend that dexamethasone be initiated with dosing every 6 h for 4 days in adult patients with suspected bacterial meningitis.4,86,87 Whereas some clinicians may consider discontinuing steroids if subsequent culture results suggest a pathogen other than S pneumoniae,94 we feel strongly that the current evidence shows that all patients with bacterial meningitis should receive steroids for the recommended 4-day course regardless of ultimate microbial diagnosis.95 Patients with septic shock and adrenal insufficiency benefit from steroid therapy in physiological doses and longer duration; however, in those with no evidence of relative adrenal insufficiency, therapy with high-dose steroids might be detrimental.86,87 There are no controlled studies of the effects of steroid therapy in a substantial number of patients with both meningitis and septic shock and, therefore, high-dose steroid therapy in that group cannot be unequivocally recommended, but the use of lower doses seems reasonable at present.86,87

One concern for steroid use is that by reducing inflammation there is a possibility that steroids may decrease permeability of the blood–brain barrier and impede penetration of antibiotics into the cerebrospinal fluid.96 Animal studies suggest that although ceftriaxone levels are not affected, cerebrospinal fluid vancomycin levels are lower in dexamethasone-treated animals.97 In human studies, treatment failure in patients with drug-resistant pneumococci treated with vancomycin and dexamethasone has also been described,98 although treatment with dexamethasone did not reduce vancomycin levels in the cerebrospinal fluid in a study of children with bacterial meningitis.99 Vancomycin as single-agent antimicrobial therapy is not currently recommended because of concerns about its efficacy against pneumococci,100 and even when used in combination with a third generation cephalosporin it is recommended that patients with pneumococcal meningitis should be carefully observed throughout therapy.9

Another concern that has been raised for steroid therapy is a possible association with long-term cognitive difficulties.101 In animal studies of bacterial meningitis, corticosteroids aggravated hippocampal apoptosis and increased the development of learning deficiencies.99 In a

Table 2: Recommended emergency department initial dose of empiric therapy for adults with suspected bacterial meningitis
long-term follow-up of the European trial that evaluated the effect of adjunctive dexamethasone therapy in adults with bacterial meningitis.94 Neuropsychological outcomes were evaluated in patients who survived pneumococcal or meningococcal meningitis.94 In 87 of 99 eligible patients, 46 (53%) of whom were treated with dexamethasone and 41 (47%) of whom received placebo, no significant differences in outcome were found between patients in the dexamethasone and placebo groups (median time between meningitis and testing was 99 months).94 These results show that adjunctive dexamethasone treatment for meningitis is not associated with an increased risk for long-term cognitive impairment in adult patients with bacterial meningitis.

Available data suggests that the timing of steroid initiation is crucial and that it needs to be administered just before or at the same time as antibiotic therapy. This recommendation is based on the treatment algorithm used by the large randomised study of adult patients who all received steroids or placebo before antibiotics,9,10 a regimen specifically chosen after data from paediatric patients found beneficial effects only in those subsets of patients who received steroids before antibiotics.9,10 Keeping this in mind, it is essential that emergency physicians understand the importance of this timing since they are most often the physicians prescribing that initial dose of antibiotics. If steroids are not given before or with the first dose of antibiotics in the emergency setting, the window of opportunity no longer exists to initiate this valuable adjunctive treatment after admission to the hospital. Therefore, emergency physicians should strongly consider administering 10 mg of dexamethasone intravenously any time they are giving antibiotics for suspected bacterial meningitis. This therapy should be initiated at the time of first antibiotic administration and continued every 6 h for 4 days.

Risk classification
Risk classification is important for establishing the level of care that a patient will require in the hospital, particularly to determine which patients should be managed in an intensive care unit or high-dependency unit. In patients with bacterial meningitis, deterioration can occur rapidly and this is difficult to predict.1 The most important factors for unfavourable outcome in adults with bacterial meningitis are those indicative of systemic compromise (ie, tachycardia, low blood pressure, positive blood culture, elevated erythrocyte sedimentation rate, or a reduced platelet count), a low cerebrospinal fluid leucocyte count, a low level of consciousness, and those indicative for infection with S pneumoniae (ie, advanced age, presence of otitis or sinusitis, presence of pneumonia, and an immunocompromised state).1,3,7 In the Dutch Meningitis Cohort, the odds of an unfavourable outcome were six times higher for patients infected with S pneumoniae when compared with patients infected with N meningitidis, even after adjustment for other clinical predictors.1 Several other prognostic factors have been described: seizures, infection by antibiotic-resistant S pneumoniae, and delays in antibiotic administration.3,15,16 Intensive care unit admission criteria have been published previously.4

Conclusions
The information reviewed in this manuscript is intended to help emergency physicians and primary-care providers who are faced with difficult diagnostic and therapeutic decisions on patients with signs and symptoms concerning for bacterial meningitis (panel). Understanding the available literature regarding these topics will assist clinicians in their approach to patient care for a potentially life-threatening infection, and a previously published algorithm for the management of patients with suspected community-acquired bacterial meningitis is presented in figure 2 to help guide decision-making.3

Conflicts of interest
We declare that we have no conflicts of interest.

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Review


